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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/707,117
Filing Date: November 06, 2000
Appellant(s): WOLFF ET AL.

Mark K. Johnson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4-28-06 appealing from the Office action mailed 8-19-04.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference

characters. The brief is deficient because it does not acknowledge that the cuff applied in Example 1 was applied while the inside of the leg was exposed; it is not readily apparent that the cuff was applied outside of the surgical area. The invention also relates to applying a cuff during an invasive surgical procedure.

(6) Grounds of Rejection to be Reviewed on Appeal

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because the examiner has withdrawn them:

New Matter

The rejection of claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been withdrawn for reasons as follows:

The rejection regarding the term "non-invasive" in claims 1 and 39 has been withdrawn. While the examples do not teach whether the ligament or cuff was applied outside of the surgical area or applied without going under the inguinal ligament as described by Milas of record (pg 2198, col. 2, lines 21-23), support for "non-invasive" is found on pg 5, line 15, of the specification as originally filed.

The rejection regarding the phrase "polynucleotide encoding a protein operably linked to a promoter in a solution" in claim 1 has been withdrawn. Pg 24, lines 9-14,

teach polynucleotides encoding proteins operably linked to promoters. Pg 23, lines 25-26, teaches injecting the polynucleotide in a saline solution.

The rejection regarding the phrase "polynucleotide encoding an expressible sequence operably linked to a promoter in a solution" in claim 39 has been withdrawn. Pg 24, lines 9-14, teach polynucleotides encoding proteins operably linked to promoters. Pg 23, lines 25-26, teaches injecting the polynucleotide in a saline solution. Pg 26, Table 1, shows the polynucleotides were "expressible."

The rejection of claim 39 under 35 U.S.C. 102(a) as being anticipated by Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364) has been withdrawn.

Von der Leyen administered naked plasmid DNA into the carotid artery of a rabbit while applying a sphygmomanometer to the skin of the limb (¶ bridging pg 2356-2357, "Transfection procedure"; pg 2360, Fig. 2, see 300). Upon further review, the procedure was as follows: a segment of the carotid artery of a rabbit was isolated using a protective sheath, a clamp was placed on the proximal end of the sheath, a catheter was advanced from the proximal end of the sheath to the distal end of the sheath, and a ligature was placed on the distal end of the sheath. The transfection solution was injected into the isolated segment of the blood vessel either under 760 mmHg of pressure (measured using a percutaneous translumenal coronary angioplasty (PTCA) manometer) or under 0-300 mmHg of pressure (measured using a sphygmomanometer).

The polynucleotide described by Von der Leyen was injected into the carotid artery and not "into a blood vessel in the limb of the mammal" as claimed.

The injecting the polynucleotide into the isolated carotid artery segment could not have resulted in delivering or expressing the polynucleotide "to the skeletal muscle cell of the limb" as claimed because the carotid artery segment was isolated by a protective sheath, a clamp at the proximal end and a ligature at the distal end and because the neck is not a limb.

Claim Rejections - 35 USC ' 103

The rejection of claims 1-3, 6, 11, 12, 16, 17, 28, 30, 31, 34, 35, 36 and 39-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Budker (1998, Gene Therapy, Vol. 5, pg 272-276) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) has been withdrawn.

Applicants argue Milas failed to cause expression in skeletal muscle cells of the limb. Applicants' argument is persuasive. One of ordinary skill would not have been motivated to replace the microvessel clips of Budker with the tourniquet of Milas because Milas did not obtain expression in skeletal muscle cells as claimed (pg 2201, col. 2, lines 16-18). As such, Milas teaches away from the claimed invention.

The rejection of claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 under 35 U.S.C. 103(a) as being unpatentable over Wolff (US Patent 6,265,387, July 24, 2001) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) has been withdrawn.

Applicants argue Milas failed to cause expression in skeletal muscle cells of the limb. Applicants' argument is persuasive. One of ordinary skill would not have been motivated to replace the microvessel clips of Budker with the tourniquet of Milas because Milas did not obtain expression in skeletal muscle cells as claimed (pg 2201, col. 2, lines 16-18). As such, Milas teaches away from the claimed invention.

Double Patenting

The rejection of claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 39-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,265,387 in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) has been withdrawn.

Applicants argue Milas failed to cause expression in skeletal muscle cells of the limb. Applicants' argument is persuasive. One of ordinary skill would not have been motivated to replace the microvessel clips of Budker with the tourniquet of Milas because Milas did not obtain expression in skeletal muscle cells as claimed (pg 2201, col. 2, lines 16-18). As such, Milas teaches away from the claimed invention.

The rejection of claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,627,616 in view of the disclosure of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) has been withdrawn.

Applicants argue Milas failed to cause expression in skeletal muscle cells of the limb. Applicants' argument is persuasive. One of ordinary skill would not have been motivated to replace the microvessel clips of Budker with the tourniquet of Milas because Milas did not obtain expression in skeletal muscle cells as claimed (pg 2201, col. 2, lines 16-18). As such, Milas teaches away from the claimed invention.

The following grounds of rejection are presented for review on appeal:

1. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 stand rejected under 35 U.S.C. 112, first paragraph, under enablement.

2. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Indefiniteness rejections labeled a)-f) remain.

3. Claim 39 stands rejected under 35 USC 102(e) as being anticipated by Draijer-van der Kaaden (US Patent 6,495,131). '131 has priority back to July 13, 1998.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Stedman's Medical Dictionary definition of "invasive"

Merriam-Webster Online Dictionary definition of "invasive"

Miller, 1995, FASEB J., Vol. 9, pages 190-199;

Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69;

Verma, Sept. 1997, Nature, Vol. 389, pg 239-242;

Crystal, 1995, Science, Vol. 270, pg 404-410; pg 409;

Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203);

Ye (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627);

Draijer-van der Kaaden (US Patent 6,495,131);

Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364);

Budker (1998, Gene Therapy, Vol. 5, pg 272-276);

Wolff (US Patent 6,265,387, July 24, 2001);

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC ' 112

Enablement

1. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a protein operably linked to a promoter and wherein said protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for applying any "non-invasive pressure" against the skin of the limb, injecting a viral vector into a blood vessel in the limb and expressing the viral vector in skeletal muscle cells as claimed or applying a cuff proximal to the site of injecting. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Breadth of claims

Claims 1 and 39 require applying non-invasive external pressure against the skin of a limb so that blood flow to and from the limb is impeded, and injecting a polynucleotide into a blood vessel in the limb in vivo distal to the applied pressure, and expressing the polynucleotide in a skeletal muscle cell in the limb distal to the applied pressure.

Claims 1 and 39 encompass using a polynucleotide that is a viral vector. Claim 3 specifically requires the polynucleotide is a viral vector.

"Invasive" is defined two different ways. 1) "denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice..." (see Stedman's Medical Dictionary definition of record) or 2) "to affect injuriously and progressively" (see Merriam-Webster Online Dictionary definition of record). Therefore, "non-invasive" encompasses any external pressure against the skin of the limb that is not applied into the body through the skin or a body orifice OR any external pressure against the skin of the limb that does not affect injuriously and progressively. Specifically, step (a) encompasses applying a tourniquet to the skin of the leg in a manner that does not affect injuriously and progressively.

The "applying" step (a) of claims 1 and 39 requires applying "non-invasive pressure against the skin of a limb" and uses open claim language. Thus, step a)

encompasses applying a tourniquet to the skin of a limb while performing a surgical procedure or while using a perfusion pump. Because of the open language, step (a) also encompasses applying a tourniquet to the skin of the leg ("non-invasively") while applying the tourniquet invasively. Therefore, if one of skill considered passing the tourniquet under the inguinal ligament during a surgical procedure "invasive", the limitation of step (a) is still met because the tourniquet also applies pressure to the skin of the limb.

The applying step (a) of claims 1 and 39 is not limited to impeding all blood flow to and from the limb. Therefore, the applying step (a) encompasses applying a tourniquet or cuff while using a perfusion pump.

The inserting step (b) of claims 1 and 39 encompasses injecting the polynucleotide by any means, including a surgical procedure and a catheter, as shown in Example 1, pg 23, lines 13-20, of the specification as originally filed or a perfusion pump.

State of the art and level of skill

It was well know and remains well known that the conditions required to target a vector to desired tissues of interest in vivo was unpredictable as supported by numerous teachings available in the art (Miller of record, 1995, FASEB J., Vol. 9, pages 190-199; Deonarain of record, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶, under Conclusion section; Verma of record, Sept. 1997, Nature, Vol.

389, pg 239-242, see entire article, pg 240, sentence bridging col. 2 and 3; and Crystal of record, 1995, Science, Vol. 270, pg 404-410; pg 409).

More specifically, Milas of record (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) shows that the conditions required to obtain protein expression in skeletal muscles of a limb using a viral vector were unpredictable. Milas applied a tourniquet to the leg of a rat passed under the inguinal ligament and injected adenoviral particles to the femoral artery and vein distal to the tourniquet using a perfusion pump (pg 2198, Fig. 1A and B, see legend and tourniquet in Fig. 1A; pg 2198, "Operative Technique"). It is noted that the tourniquet passed over all blood vessels of the leg including the femoral artery and vein (pg 2199, Fig. 2). The tourniquet passed under the inguinal ligament described by Milas is "non-invasive" as claimed because it contacts the skin and does not affect the leg injuriously or progressively, thus meeting one definition of "non-invasive." Applying a tourniquet as described by Milas also meets the limitation of step (a) because step (a) uses open language and does not exclude applying pressure against the skin while passing the tourniquet under the inguinal ligament; step (a) is not limited to applying pressure only against the skin. Applying a tourniquet as described by Milas also meets the limitation of "impeding blood flow into and out of the limb" in step (a) because step (a) uses open language and does not exclude partially impeding blood flow into and out of the leg using a tourniquet while using a perfusion pump and because the tourniquet blocks blood flow between the leg and the rest of the body; step (a) is not limited to impeding <u>all</u> blood flow into and out of the leg. Therefore, the steps of applying a tourniquet and injecting an adenoviral vector taught by Milas are within the

metes and bounds of steps a) and b) of claims 1 and 39. However, the method of Milas did not result in expression of protein in skeletal muscle cells distal to the applied pressure as claimed (pg 2201, col. 2, 1st full ¶). Therefore, one of skill would have recognized that not all methods of applying a tourniquet and injecting a polynucleotide into a blood vessel encompassed by steps (a) and (b) would result in expression of the polynucleotide as claimed.

Ye of record (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) administered adenoviral particles encoding LacZ retroorbitally while the portal vein/artery was occluded with clamps; the method did not result in expression in skeletal muscle (pg 623, col. 2). Thus, while Ye did not administer the adenoviral particles to the limb or apply pressure "non-invasively" as claimed, Ye supports the fact that one of skill would not necessarily know how to deliver adenoviral vectors to a blood vessel and obtain expression in skeletal muscle cells (pg 621, 1st full paragraph).

Examples and Teachings in the specification

Example 1 in the specification teaches making an incision in the limb of a monkey, placing a catheter into an artery anterogroadely, impeding blood flow using a sphygmomanometer cuff surrounding the limb proximal to the injection site. The sphygmomanometer was inflated and papaverine was injected into the catheterized artery followed by naked plasmid DNA encoding a marker protein operably linked to a promoter (pg 23, lines 13-26). Expression was obtained in skeletal muscles (pg 25, line 29, through pg 28, line 3). Example 8 on pg 31 does not require applying pressure

"non-invasively" as claimed. The method in Example 9 cannot be determined because it merely states the solution was injected "as described in Examples above" without stating the method of Example 1 was used.

The specification suggests using a viral vector, specifically an adenoviral vector (pg 15, line 14). However, the specification does not provide any teachings for one of skill to overcome the teachings of Milas or provide any examples of injecting an adenovirus while applying a sphygmomanometer cuff or tourniquet to the skin.

Amount of experimentation

One of skill would recognize that steps (a) and (b) as claimed encompass the steps taught by Milas but would not result in expression as claimed. Given the breadth of steps (a) and (b) taken with the teachings of Milas and the lack of teachings in the specification regarding how to overcome the teachings of Milas and obtain expression in skeletal muscle cells using adenovirus, it would have required one of skill undue experimentation to determine how to perform the steps of (a) and (b) as broadly claimed using an adenovirus and obtain expression as claimed. While non-operative embodiments are allowed in a claim, steps that are not enabled in the specification as originally filed are not. The steps in the methods claimed do not exclude using a perfusion pump while applying a tourniquet. As such, the steps in the methods claimed encompass the steps of Milas and, therefore, encompass non-enabled steps. No amount of experimentation would allow one of skill to obtain expression of an

adenovirus in skeletal muscle cells by applying a tourniquet while using a perfusion pump as encompassed by the claims.

Indefiniteness

2. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

a) The phrase "to a skeletal muscle cell of a mammal" in the preamble in claim 1 is not commensurate in scope with the phrase "to the skeletal muscle cell in the limb distal to the applied pressure" in step c of claim 1. The phrase "the skeletal muscle cell in the limb distal to the applied pressure" in step c of claim 1 lacks antecedent basis. It is unclear if the claim is intended to deliver the polynucleotide to any skeletal muscle cell of mammal as in the preamble or to a skeletal muscle cell of a limb distal to the site of applying pressure as in the body of the claim.

b) Claim 1, step b), as newly amended is indefinite because the phrase "inserting the polynucleotide encoding a protein operably linked to a promoter in a solution into a blood vessel" lacks antecedent basis. The phrase in the body of the claim is not readily apparent from the preamble of the claim, which merely refers to "delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo."

c) The phrase "applying non-invasive external pressure" in claim 1 and "applying pressure non-invasively" in claim 39 remain indefinite for reasons of record.

"Invasive" can be defined two different ways. 1) "denoting a procedure requiring insertion of an instrument or device into the body through the skin or a body orifice..." (see Stedman's Medical Dictionary definition attached) or 2) "to affect injuriously and progressively" (see Merriam-Webster Online Dictionary definition attached). The specification does not teach which scope to use. It is not readily apparent that the methods used by applicants do not require inserting an instrument into the body through the skin because the cuff described in Example 1 was applied during a surgical procedure. It is not readily apparent that the cuff was applied outside of the surgical area (only on skin) and not over the surgical area. Therefore, it cannot be determined whether pressure that does not cause injury to the leg is encompassed by the phrase. Nor can it be determined if a tourniquet that passes under the inguinal ligament in a surgical area is non-invasive because such a tourniquet does not affect the leg injuriously or progressively.

d) The phrase "wherein said applying, said inserting, said delivering and said expressing the polynucleotide do not diminish subsequent use of the limb by the mammal" as newly amended in claim 39 remains unclear. It is unclear if the phrase is limited to the function of the limb after the procedure or if the phrase encompasses the diminished frequency of use of the limb. Pg 3, lines 13-19, and pg 25, lines 17-25, do not clarify the issue. Pg 3 refers to maintaining the function of the limbs after delivery of polynucleotides and applying pressure. Pg 25, lines 17-25, also refers to maintaining the function of the limbs after delivery of polynucleotides and applying pressure. It is not readily apparent from the specification that pg 3 or pg 25 encompasses the

frequency of use of the limb. Pg 22, lines 26-29, teach obtaining minimal intimal changes in the arteries were observed but does not discuss the effect of the surgery or gene expression on the function or frequency of use of the limb. Pg 25, lines 17-20 teaches monkeys had full function of the limbs but does not teach the monkeys used their limbs as frequently as before the surgery. Pg 25, lines 22-24, teaches the monkeys were not in any discomfort but does not teach the monkeys used their limbs as frequently after surgery. In fact, contrary to the claim, it was well known that a limb that underwent surgery had diminished use right after surgery because of inflammatory responses, anesthesia and pain. Thus, the metes and bounds of the phrase are unclear and do not make sense when considering surgery recovery.

e) The phrase "the polynucleotide encoding an expressible sequence operably linked to a promoter in a solution" in claim 39, step b) lacks antecedent basis.

f) The phrase "the skeletal muscle cell of the limb distal to the applied pressure" in step b) of claim 39, lacks antecedent basis.

Claim Rejections - 35 USC ' 102

3. Claim 39 remains rejected under 35 USC 102(e) as being anticipated by Draijer-van der Kaaden (US Patent 6,495,131). '131 has priority back to July 13, 1998.

Draijer-van der Kaaden administered adenovirus encoding LacZ operably linked to a promoter into the femoral vein of a rat using a perfusion pump while applying a tourniquet around the groin (detailed description, ¶ 25; col. 16, line 65, through col. 17, line 55). The procedure was as follows: an incision was made in the leg of a rat next to

the inguinal ligament, a plastic tube was inserted into a blood vessel (part of the perfusion pump), and branching blood vessels were "occluded by the application of a tourniquet around the groin" (col. 17, lines 1-8). The "circuit" (the tube of the perfusion pump and the blood vessels of the leg) was perfused for 3 minutes to wash out the blood of the leg (lines 10-14). The adenovirus was then perfused through the leg for 5-30 minutes (lines 15-20). LacZ expression occurred in skeletal muscle cells of the leg (Table II, col. 18).

Applying the tourniquet to the groin as taught by Draijer-van der Kaaden is equivalent to "applying pressure non-invasively against the skin of a limb" as claimed because it did not injure the leg and because Draijer-van der Kaaden did not teach the tourniquet went under the blood vessel.

The tourniquet applied to the groin as taught by Draijer-van der Kaaden impedes "blood flow to and from the limb" as claimed because "[c]ollaterals were temporarily occluded by the application of a tourniquet around the groin" (col. 17, lines 6-8). "Collaterals" refers to branching blood vessels of the leg, i.e. both arteries and veins, that provide blood flow both to and from the leg as claimed. The "applying" step (a) is not limited to impeding **all** blood flow to and from the limb; step (a) encompasses partially impeding blood flow to and from the limb. The "inserting" step (b) uses open language and encompasses inserting the polynucleotide using a perfusion pump; step b) does not exclude inserting the polynucleotide using a perfusion pump. As such, claim 39, steps a) and b) encompasses applying a tourniquet to branching blood vessels of the leg so that some blood flow to and from the limb is occluded while

injecting adenovirus into a blood vessel of the leg using a perfusion pump distal to the tourniquet as described by Draijer-van der Kaaden.

The perfusion pump was inherently inserted distal to the tourniquet around the groin as claimed because the tourniquet was applied to the groin and the adenovirus was injected into the blood vessel in the leg and because gene expression occurred in the leg muscles. This is equivalent to the "inserting the polynucleotide... ...distal to the applied pressure" in claim 39, step b.

The polynucleotide was expressed in skeletal muscles of the leg (col. 18, Table II) distal to the tourniquet applied to the groin. This is equivalent to steps c) and d) of claim 39.

(10) Response to Argument

1. Enablement:

Applicants argue Miller, Deonarain, Verma and Crystal were published prior to the instant application and do not contemplate the method described by applicants. Therefore, applicants conclude that Miller, Deonarain, Verma and Crystal do not apply to applicant's process. Applicants' argument is not persuasive. Miller, Deonarain, Verma and Crystal establish the state of the art of gene transfer. Furthermore, the method described by applicants in the specification is not at issue. The claims are not enabled for their full breadth because they use open language and encompass applying a tourniquet to the skin while passing it under the inguinal ligament during a surgical

procedure and using a perfusion pump to deliver adenovirus as taught by Milas who taught such a method did not provide delivery to skeletal muscle cells as claimed.

Applicants argue Milas cannot apply because claims 1 and 39 require impeding blood flow to and from the limb. Applicants' argument is not persuasive. The claims do not require impeding all blood flow to and from the limb. The claims use open language and encompass applying a tourniquet to the skin so that blood flow to and from the limb is impeded while using a perfusion pump. The tourniquet described by Milas impedes blood flow both to and from the limb as claimed. This is all that is required to meet the limitation of step (a).

In the last sentence bridging pg 5-6 of the appeal brief applicants argue the differences between the process of Milas and the one described by applicants account for the difference in delivery to skeletal muscle. Applicants' arguments are moot because steps a) and b) of claims 1 and 39 use open language and do not reflect the differences between the process of Milas and the one described in the specification.

The first full paragraph on pg 6 of the appeal brief cites a comment made by the examiner about claim interpretation and argues the claim states pressure is applied non-invasively to impede blood flow. In response, it is noted that steps a) and b) of claims 1 and 39 use open language and can be interpreted broadly as encompassing applying a tourniquet to the skin such that blood flow into and out of the limb is impeded and passing the tourniquet under the inguinal ligament.

The second full paragraph on pg 6 of the appeal brief argues the breadth of claims 1 and 39 is limited to impeding all blood flow to and from the limb. Applicants

point to pg 30, lines 23-24, which states that failure to occlude blood flow results in no delivery. Applicants point out that Milas allowed outflow using a perfusion pump. Applicants' arguments are not persuasive. Steps a) and b) of claims 1 and 39 use open claim language and encompass partial occlusion or occluding blood flow to and from the leg using a tourniquet combined with using a perfusion pump.

Applicants argue Ye taught injection of adenovirus retroorbitally and not intraportally. Therefore, applicants conclude Ye did not apply to the instant application. Applicants' argument is not persuasive. Ye specifically states in the first paragraph that the parameters required to target adenovirus to the tissue of interest by injection into the blood vessel was unknown. Ye has been cited to establish the unpredictability of the art at the time of filing.

Applicants point to the declaration filed 5-9-03, which was found unpersuasive because the teachings in the declaration were not present in the specification and were essential to perform the method using adenovirus. Applicants argue the teachings in the declaration were present in the specification as originally filed. Applicants' arguments are not persuasive.

The combination of elements required to target the tissue of interest using adenovirus is essential to the claimed invention (based on Miller, Verma, Crystal, Deonarain, and Ye all of record). The specification suggests using papaverine (pg 5, lines 26-28; ¶ bridging pg 16-17) and "an enzyme [that] could digest the extracellular material" (¶ bridging pg 16-17). It is not readily apparent from the specification that applicants considered using both papaverine and collagenase as described in the

declaration because the paragraph bridging pg 16-17 and pg 5, lines 26-28 only suggest using one compound that is papaverine or an enzyme and because Examples 1 and 8 only used papaverine.

Applicants argue the specification does not imply that only one of the provided list of possible agents may be used. Applicants argue one skilled in the art would consider the possibility of success in combining multiple agents that work by different mechanisms. Applicants' arguments are not persuasive. It is not readily apparent that applicants contemplated using more than one agent. Pg 5, lines 26-28, or pg 16, line 19, to pg 17, line 7, only suggest using "an agent". It is not readily apparent that one skilled in the art would have considered combining agents that worked by different mechanisms. As such, it is not readily apparent that applicants originally contemplated combining papaverine and an enzyme together as described in the declaration filed 5-9-03.

Applicants argue injecting $5x10^8$ adenoviral particles was within the realm of routine experimentation. Applicants argue one of skill could estimate the number of adenoviral particles needed based on the number of plasmid molecules injected in example 8, which is well above $5x10^8$. Applicants' argument is not persuasive. When the state of the art is so unpredictable that one of skill could not determine how to target adenoviral particles to the tissue of interest, the dosage is essential to the invention. It is not readily apparent that $\underline{5x10^8}$ was within the realm of routine experimentation from the specification as originally filed. Furthermore, the amount of plasmid does not

correlate to the adenoviral viral titer because the vectors have different mechanisms of action.

Applicants argue the method in the declaration represents the breadth of claims 1 and 39 as it relates to viral vectors. Applicants' argument is not persuasive. The claims do not require treatment with papaverine and collagenase or injecting the solution within 10 seconds as described it the declaration. The specific combination of parameters in the declaration does not support the broad genus claimed. Furthermore, the specific combination of papaverine and collagenase is not readily apparent from the specification as originally filed.

Applicants argue the specification described delivering 10 ml of plasmid in 10 seconds on pg 31, lines 11-12, which is adequate to support delivering 10 ml of adenovirus in 10 seconds. While delivering adenovirus rapidly is encompassed by the specification as originally filed (pg 4, lines 27-33, taken with pg 15, line 14), the specification as originally filed did not contemplate combining rapid delivery with papaverine and collagenase and adenovirus as described in the declaration. Furthermore, the claims do not require rapid delivery or delivery within 10 seconds.

Overall, Example 8 does not correlate to the results described in the declaration because example 8 required plasmid DNA and did not use collagenase while the declaration taught injecting $\underline{5x10^8}$ adenoviral particles/10 ml saline within 10 seconds after papaverine and collagenase. It is not readily apparent that merely replacing the plasmid in Example 8 with $5x10^8$ adenovirus would provide the results described in the declaration, which required both papaverine and collagenase. The concentration of

$5x10^8$ adenoviral particles/10 ml saline described in the declaration is not taught anywhere in the specification and is not readily apparent from the teachings of the specification. Pg 17, line 9, to pg 18, line 6, only describe the injection volume (ml, ml/body weight, ml/liver weight or ml/limb muscle weight) and the speed at which a vector is injected. Pg 17, line 9, to pg 17, line 25, does not correlate to the results described in the declaration because they are limited to injection volumes for non-viral vectors. In conclusion, the specification does not reasonably lead one of skill to the conclusion that applicants contemplated injecting $5x10^8$ adenoviral particles after papaverine and collagenase at the time of filing. Therefore, the specification as originally filed did not teach the essential elements required to obtain the results described in the declaration.

2. Indefiniteness:

a). The phrase "to a skeletal muscle cell of a mammal" in the preamble in claim 1.

Applicants argue the preamble must be read while considering the limitations in the rest of the claim. Therefore, applicants conclude the claim is unambiguous. Applicants' argument is not persuasive. It is unclear if the claim is intended to deliver the polynucleotide to any skeletal muscle cell of mammal as in the preamble or to a skeletal muscle cell of a limb distal to the site of applying pressure as in the body of the claim. The preamble should have a clear nexus with the body of the claim so that one of skill could determine when the final step had been reached. In this case, the

preamble does not have a nexus with the body of the claim, thus making the claims ambiguous.

b) The phrase "inserting the polynucleotide encoding a protein operably linked to a promoter in a solution into a blood vessel" lacks antecedent basis in claim 1, step b).

Applicants argue the phrase has antecedent basis in the preamble. Applicants' argument is not persuasive. The phrase in the body of the claim is not readily apparent from the preamble of the claim, which merely refers to "delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo." It is not apparent that the polynucleotide in the in preamble encodes a protein operably linked to a promoter.

c) The phrase "applying non-invasive external pressure" in claim 1 and "applying pressure non-invasively" in claim 39.

Applicants argue the metes and bounds of the phrases are clear "for reasons already stated in response to the previous 112, first paragraph, rejections" (pg 9, 3rd full ¶, of appeal brief). Applicants' argument is not persuasive. The enablement arguments do not address the metes and bounds of "non-invasive" or the two definitions of "invasive" cited by the examiner. It is not readily apparent that the methods used by applicants were without injury because applicants performed the method by making an incision and inserting a catheter (Example 1). It is not readily apparent that the cuff described in Example 1 was applied outside of the surgical area (only on skin) and not over the surgical area. Nor can it be determined if a tourniquet that passes under the

inguinal ligament in a surgical area without affecting the leg injuriously or progressively is within the metes and bounds of what applicants consider non-invasive.

d) The phrase "wherein said applying, said inserting, said delivering and said expressing the polynucleotide do not diminish subsequent use of the limb by the mammal" in claim 39.

Applicants argue the specification taught the monkeys "did not appear to be in any discomfort beyond that of normal surgical recovery (pg 25, lines 22-24). Applicants' argument is not persuasive. The passage on pg 25 uses the term "recovery" which implies that full use of the limb must be "recovered." It was well known in the art that a limb that underwent surgery has temporary loss of function. Therefore, the phrase as written does not make sense.

e) The phrase "the polynucleotide encoding an expressible sequence operably linked to a promoter in a solution" in claim 39, step b).

Applicants argue the phrase has antecedent basis in the preamble of the claim. Applicants' argument is not persuasive. The phrase in the body of the claim is not readily apparent from the preamble of the claim, which merely refers to "delivering a polynucleotide to a skeletal muscle cell of a mammal in vivo." It is not apparent that the polynucleotide in the in preamble encodes an expressible sequence operably linked to a promoter.

f) The phrase "the skeletal muscle cell of the limb distal to the applied pressure" in step b) of claim 39.

Applicants argue the phrase has antecedent basis in the preamble of the claim. Applicants' argument is not persuasive. The phrase in the body of the claim is not readily apparent from the preamble of the claim, which merely refers to "a skeletal muscle cell of a mammal in vivo." It is not apparent that the skeletal muscle cell in the in preamble is distal to the applied pressure as in the body of the claim. The preamble and the body of the claim should have a clear nexus.

3. 102 over Draijer-van der Kaaden:

Applicants argue the tourniquet restricted the adenovirus to certain tissues to avoid unnecessary infections and cite col. 6, lines 25-30, of Draijer-van der Kaaden. Applicants' argument is not persuasive. It is irrelevant why Draijer-van der Kaaden used the tourniquet because Draijer-van der Kaaden applied the tourniquet to the groin of the rat non-invasively as claimed, injected adenovirus distal to the tourniquet and obtained expression in skeletal muscle cells of the leg.

Applicants argue the tourniquet did not "prevent blood flow out of the limb, since '131 taught that perfusion was performed by creating a closed circuit and repassing the adenovirus through the isolated tissue (col. 10 lines 45-55). Applicants' argument is not persuasive. The tourniquet applied to the groin impedes "blood flow to and from the limb" as claimed because "[c]ollaterals were temporarily occluded by the application of a tourniquet around the groin" (col. 17, lines 6-8). "Collaterals" (col. 17, line 6) refers to branching blood vessels of the leg, i.e. both arteries and veins, that provide blood flow both to and from the leg as claimed. Claim 39, step a, is not limited to occluding all

blood flow to and from the limb. The "inserting step" b) of claim 39 does not exclude using a perfusion pump to insert the polynucleotide. As such, claim 39, steps a) and b) encompasses applying a tourniquet to branching blood vessels of the leg so that some blood flow to and from the limb is occluded while injecting adenovirus into a blood vessel of the leg using a perfusion pump distal to the tourniquet as described by Draijer-van der Kaaden.

The closed circuit mentioned in col. 10, lines 45-55, in col. 11, lines 26-27, and in col. 17, Example 3, and cited by applicants on pg 10 of the appeal brief, refers to the perfusion pump. Applicants' argument is not persuasive because claim 39 encompasses applying a tourniquet while injecting adenovirus into a blood vessel of the leg using a perfusion pump for reasons cited in the paragraph above.

"Applicants disagree and, moreover, do not understand how the claims can be interpreted to encompass forming a vascular closed circuit through which fluid is circulated using a perfusion pump as described in the '131 patent" (pg 10 of appeal brief). Claim 39, step a, is not limited to occluding all blood flow to and from the limb. The "inserting step" b) of claim 39 does not exclude using a perfusion pump to insert the polynucleotide. As such, claim 39, steps a) and b) encompasses applying a tourniquet to branching blood vessels of the leg so that some blood flow to and from the limb is occluded while injecting adenovirus into a blood vessel of the leg using a perfusion pump distal to the tourniquet as described by Draijer-van der Kaaden.

Applicants point out that "'administration via the circulation mainly transduced endothelial cells of the tumor vasculature' (column 12, lines 20-21), 'gene transfer into

tissues other than the tumor hardly occurs using either method' (isolated limb perfusion or direct tumor injection, column 12 lines 23-24), staining of tissues showed color (i.e., expression product) 'was restricted to areas directly adjacent to the blood vessels of the tumor' and not even in the tumor itself (column 18 lines 47-50), and 'no high uptake of (adenovirus) by the liver or skeletal muscle of the isolated limb after ILP or intra-tumor injection (column 18 lines 19-22)." Applicants' arguments are not persuasive. Applicants have mixed tumor expression analysis with skeletal muscle expression analysis. Table II in col. 18 clearly shows that expression of LacZ occurred in skeletal muscle as claimed. The amount of expression obtained is irrelevant and is not distinguished in step d) of claim 39.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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